

REMARKS/ARGUMENTS

Status of the claims

Claims 7, 8, 11, 12, 22, 23, and new claims 26-39 are pending. Claim 8 is amended to delete certain embodiments, which now appear in new claims 26-30. Similarly, claims 12 and 23 are amended to delete certain embodiments, which now appear in new claims 31-33, and 34-39, respectively. No new matter is added.

Specification

The Examiner has maintained the objections to the specification, alleging that the amendments submitted with the December 21, 2009 Response were non-compliant. In support of this allegation, the Examiner cites 37 CFR 1.121(b)(ii) for deleting 5 or fewer characters with double brackets.

Regarding the heading for the Brief Description of the Drawings, Applicants respectfully note that the heading includes more than 5 characters, and thus the deletion is indicated with a strike-through. The intention of the Applicants is to delete the heading.

Regarding the citation on page 16, line 12, the citation is complete. The reference consists of a single page, that is, page 5081. The “-xxxx” term consists of 5 characters, and thus the deletion is indicated with double brackets, as set forth in Rule 121(b)(ii). The intention of the Applicants is to delete the -xxxx term.

Regarding the term Proventil in paragraph 133, starting on page 37, line 9, Applicants respectfully submit that the term was capitalized and followed by generic language in the December 21 2009 Response, as requested by the Examiner. With the present response, a ® mark is included to be absolutely clear. Deletion of the previous language “Proventil.quadrature.” was indicated with a strike-through because it is more than 5 characters. The remaining amendments to the paragraph are also in compliance with Rule 121(b)(ii), that is, deletion of the term consisting of 4 characters is indicated with double brackets and deletion of the terms consisting of 9 and 46 characters (no spaces) are indicated with strike-throughs.

Finally, the Examiner asserts that the specification fails to provide antecedent basis for the term “anti-inflammatory.” The term has been added to paragraph 19. Support is found in original claims 12 and 25 (*see* MPEP 2163.06).

Applicants respectfully submit these amendments in a good faith effort to address the Examiner’s concerns. If outstanding issues with the specification remain, Applicants respectfully request that the Examiner contact the Applicant’s representative by telephone.

Rejection under 35 USC § 112, first paragraph – Enablement

Applicants gratefully acknowledge the withdrawal of the previous rejection of the claims as allegedly obvious based on disclosures relating to pyocins. In the present action, the Examiner has rejected claims 7, 8, 11, 12, 22, and 23 as allegedly lacking enablement, again, based on disclosures relating to pyocins. On page 9 of the Office Action, the Examiner alleges that the specification does not provide a working example of treating a subject or eukaryote, but notes the *in vitro* data disclosed in the specification, *i.e.*, that the phage tails effectively kill a much higher percentage of *Staphylococcus* isolates than intact phage.

Applicants respectfully traverse the rejection for the reasons set forth in detail below. In brief, the cited art shows that pyocins can have variable effects *in vitro* and *in vivo*, but is silent on the therapeutic effect of phage tails for reducing a bacterial population in an infected subject. Phage tails, however, are not pyocins. Prediction of the killing activity of a phage tail based on a direct comparison to the killing activity of pyocins is therefore not valid. Moreover, the cited pyocin disclosures do not cast doubt on the correlation between *in vitro* and *in vivo* killing activity of the defined dose bacteriocidal agent as recited in the claims.

Legal standard

It is axiomatic that an enabling disclosure must teach one of skill in the art to practice the invention without undue experimentation (*see* MPEP 2164.01). MPEP 2164.02 explains that the lack of a working example should never be the sole reason for rejecting a claimed invention if the disclosure otherwise complies with that standard. In addition, an *in vitro* example can constitute a working example if that example correlates with the claimed method

invention. Correlation is dependent on the state of the prior art, so that if a particular model is recognized as correlating to a specific condition, it should be accepted as correlating absent evidence that the model does not correlate. The Federal Circuit has stated that exact correlation is not required, as long as there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity.

Pyocins are distinct from phage tails

The Examiner's position is that use of a phage tail to kill bacteria *in vivo* is unpredictable. The Examiner bases this assertion on references that discuss pyocin killing activity, and then seeks to link pyocins to phage tails. To establish this link, the Examiner points to a statement in paragraph [0008] of the present specification to assert that "pyocins are tail-like preparations" and to Shinomiya, cited in the August 25, 2009 Office Action, to assert that *in vitro* killing activity of phage tails is similar to that of R-type pyocins.

To clarify, paragraph [0008] states that pyocins "are believed to be tail-like portions of tailed phages," and continues to explain that the relationship of pyocins to phage is not well understood. While Shinomiya compares pyocins and phage tails, the reference actually distinguishes the two both structurally and functionally, as explained below.

The art cited by the Examiner to cast doubt on the *in vivo* efficacy of phage tails is thus not on point – it relates to pyocins. The cited pyocin art, primarily from the 1970's, shows that investigators using various methods of *in vivo* administration observe variable results. The references essentially provide a snapshot of the state of art 35 years ago for therapeutic use of pyocins.

The cited art does not invalidate the correlation between *in vivo* and *in vitro* killing activity

Even if one were to accept the similarity of pyocins and phage tails, pyocins have been shown to effectively protect animals from bacterial infections as long as the pyocins are administered soon after challenge, *i.e.*, when the population of bacteria is relatively small. As explained in the present specification, one of the advantages of the invention is that non-replicative phage tails provide a defined dose of bacteriocidal agent. For treatment of an existing

bacterial infection, *i.e.*, where the bacterial population is relatively large, one of skill would understand that a higher dose would be necessary. The pyocin references do not cast doubt on the idea that a higher dose of pyocin may be effective for treating an existing bacterial infection *in vivo*, as the references do not describe use of sufficiently high doses of pyocins to be effective at later time points in the bacterial infection.

Applicants will briefly summarize the cited references and then explain why these disclosures do not cast doubt on the claimed invention.

Merrikin *et al.* (1972) *Applied Microbiol.* 23:164

On page 10 of the present Office Action, the Examiner asserts that Merrikin teaches that pyocin 78-C2 is not effective for treating existing *P. aeruginosa* infection in mice.

Applicants respectfully disagree, as Merrikin discloses that pyocin *is* effective when administered IV immediately after infection or within 6 hours, but it is not effective when administered IV at the same dose 24 hours after infection. Given 18 additional hours to expand, even if it were at less than an exponential rate, the bacterial population at 24 hours would be quite large.

In general, however, Merrikin provides very little detail about the experiments, such as the type or amount of pyocin used. One of skill would not conclude from this sparse disclosure that the present invention would not work as claimed.

Williams (1976) *J. Med. Microbiol.* 9:153

On page 11 of the Office Action, the Examiner asserts that Williams teaches that pyocins are effective for killing *P. aeruginosa in vitro*, but not for treating an existing infection *in vivo*. Williams describes IP administration of pyocins concurrently, 3 hours after, or 6 hours after bacterial infection. Only concurrent administration was effective. This may not be surprising, given the fact that the same dose of pyocin was used regardless of the stage of bacterial infection, but the results are different from those described in Merrikin.

Williams also describes topical use of pyocins on bacterially-infected burns. Williams reports that the number of bacteria on the burns was not significantly reduced with pyocin treatment, but does not report when this count was carried out relative to infection and treatment. In the end, however, 7 of 14 bacterially-infected mice that received the pyocins

survived, while only 4 of the 14 untreated, bacterially-infected mice survived. This 75% increase in the number of surviving animals is actually remarkable, considering that bacteria administered to a burn will rapidly enter the bloodstream and expand beyond the reach of a topical treatment.

Haas et al. (1974) J. Infectious Diseases 129:470

On page 11 of the present Office Action, the Examiner asserts that Haas teaches that a pyocin effective *in vitro* had no effect on the mortality of mice infected with *P. aeruginosa*. Contrast page 6 of the Office Action of August 25, 2009, where the Examiner alleged that Haas teaches that a pyocin is protective against *P. aeruginosa* infections in mice, and that *in vitro* susceptibility to pyocin reliably correlates with *in vivo* protective effect.

Haas indicates that pyocins have a prophylactic, but not a therapeutic, effect on bacterial infections in mice. Similar to Williams, Table 1 of Haas shows that pyocin injection prior to bacterial challenge reduced mortality significantly, while injection one hour after bacterial challenge did not reduce mortality (unlike Merrikin). The pyocin dose was the same regardless of the course of the bacterial infection, so the apparent ineffectiveness of the pyocin may not be surprising considering that bacterial doubling time is in the range of 25 minutes (see paragraph [0194] of the present specification).

Skurnik and Strauch (2006) Int'l J. Med. Microbiol. 296:5

On page 12 of the Office Action, the Examiner cites Skurnik as stating that phage tail-like bacteriocins will likely be limited to *in vitro* applications. Skurnik focuses on therapeutic use of phage, but does briefly review a more recent report of effective use of a bacteriocin to reduce bacterial infection when administered orally shortly after infection. As with the other reports, the bacteriocin was reportedly not effective for treating an existing bacterial infection.

Applicants again emphasize that bacteriocins (which include pyocins) are described as "tail-like," but have been described as structurally and functionally distinct from phage tails.

Shinomiya et al. (1979) J. Virology 32:958

Shinomiya was cited in the August 25, 2009 Office Action, and is cited on page 10 of the present Office Action as teaching that the killing activity of phage tails is similar to that of R-type pyocins.

Shinomiya does state that phage tails and pyocins use a similar “single-hit” mode of action (Shinomiya, Abstract). The defined dose aspect of the present invention is an advantage, because the amount of circulating bacteriocidal agent can be precisely controlled and monitored. The phage tails do not replicate.

Shinomiya, however, also describes the structural differences between R-type pyocins and phage, and concludes that pyocins are not directly derived from phage (Shinomiya, page 966). Shinomiya also teaches that while the disclosed phage tails and pyocins both target *P. aeruginosa*, they have a different strain specificity, indicating differences in structure and function.

Summary of the cited art

In summary, the art discloses attempts to treat different types of bacterial infections using different pyocins in different preparations and modes of administration. Generally, the pyocins are shown to be ineffective when administered after the infection is established, though there is some variability in the timing.

The Examiner's position relies on the validity of equating pyocins with phage tails, and concluding that *in vitro* activity does not always correlate with *in vivo* activity. As explained by Shinomiya, and in the December 21, 2009 response, there are differences between phage tails and pyocins.

Moreover, the Examiner fails to establish that *in vitro* killing activity is not correlated with *in vivo* therapeutic activity. For the most part, the pyocins described in the references were able to kill bacteria both *in vitro* and *in vivo*, but use of an increased amount of pyocins was not tested in more established infections. This is a problem actually solved by the present inventors who recognized that a defined dose bacteriocidal agent would be advantageous, and could be used to treat an established bacterial infection when present in sufficient quantities.

The claimed *in vivo* methods are supported by reasonably correlated *in vitro* results

The present invention is based in part on the recognition that a non-replicative phage tail can provide the advantage of a defined dose. The inventors recognized that the dose of the phage tail administered to treat an existing infection must be commensurate with the bacterial population. This concept is set forth in the Introduction, on page 10, paragraphs [0041]-[0042] of the specification as filed. Page 36, paragraph [0130] also explains that the dosage will depend on the site and extent of bacterial colonization.

The importance of the dose for a non-replicative bacteriocidal agent was not appreciated by the cited art. The cited art shows that, in general, pyocins can effectively kill bacteria *in vivo* and *in vitro*, but that the same dose was not effective for eliminating established infections *in vivo*, comprising a larger, expanding bacterial population.

The Examples disclosed in the specification show that phage tails from different parent phage can effectively kill multiple bacterial strains *in vitro*. The specification also explains how to prepare and administer phage tail compositions in prophetic Example 9, as well as pages 32-34 and 36-39. One of skill would not have any objective reason to doubt that an appropriate dose of phage tails could reduce a bacterial population *in vivo*.

One of skill in the art, given the present description of defined dose phage tails, supported by the extensive *in vitro* data, would not face undue experimentation in practicing the claimed methods of treatment. In view of the foregoing, Applicants respectfully request withdrawal of the rejection under the first paragraph of 35 USC § 112 for enablement.

Provisional rejection for non-statutory double patenting

The Examiner has rejected claims 7, 8, 11, 12, 22, and 23 as allegedly unpatentable for non-statutory double patenting based on USSN 11/915,272. The claims of the '272 application and the present application have yet to be finalized. Applicants will consider filing a terminal disclaimer once the pending claims are considered otherwise allowable (*see* MPEP 804).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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